REMARKS

Claims 1-5, 29-36, 40-52, and 54-59 are pending the instant application. No amendments have been made. Accordingly, Claims 1-5, 29-36, 40-52, and 54-59 are presented for further examination in view of the forgoing remarks.

In view of Applicants' amendment and remarks filed December 31, 2008, all outstanding rejections have been overcome. The following new grounds of rejection were not necessitated by the amendment. Accordingly, the Office Action is non-final.

As an initial matter, Applicants note that Claims 38 and 39 were previously cancelled. Claims 42-44 have not been rejected.

Rejection of Claims under 35 U.S.C. §103(a)

Claims 1-5, 29, 30, 33-35, and 38-41 were rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Zajac *et al.*, *Int. J. Cancer* (1997) 71:491-496 ("Zajac") in view of Kawakami *et al.*, *J. Immunother.* (1998) 21(4):237-246) ("Kawakami").

In addition, Claims 1-5, 29, 30, 33, 34, 36, and 38-41 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Kittlesen *et al. J. Immunol.* (1998) 160:2099-2106 ("Kittlesen") in view of Kawakami.

Claims 1-5, 29-32, 35, and 38-41 were rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Jäger *et al.*, *J. Exp. Med.* (1998) 187:265-270 ("Jäger") in view of Kawakami.

Finally, Claims 45-52 and 54-59 were rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Zajac in view of Kawakami, Jäger, and Tsuji *et al.*, *Int. J. Immunopharmacology* (1998) 20(1-3):111-124 ("Tsuji").

Applicants respectfully disagree that the cited references, either alone or in combination, render the pending claims obvious as discussed below.

Standard for Obviousness

The Patent and Trademark Office has the burden under section 103 to establish a *prima facie* case of obviousness. *In re Piasecki*, 745 F.2d 1468, 1471-72, 223 USPQ 785, 787-87 (Fed. Cir. 1984). An essential characteristic of any *prima facie* case of obviousness is that the references, when combined must teach or suggest all the claim limitations. See M.P.E.P. §2143. Furthermore, the U.S. Supreme Court has made clear that there must be some perceptible reason to modify the prior art to arrive at the claimed invention. Rejections on obviousness cannot be sustained by mere conclusory statements; instead there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness. *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398, 127 S. Ct. 1727, 82 USPQ.2d 1385 (2007), cited in MPEP 2143.01. Further, "[o]bviousness cannot be predicated on what is unknown." *In re Spormann*, 363 F.2d 444, 448, 150 USPQ 449, 452 (CCPA 1966). It is impermissible hindsight to use the present application as a template to piece together prior art teachings to allege obviousness. *See In re Fritch*, 972 F.2d 1260, 1266 (Fed. Cir. 1992).

The Claims

The claims relate to compositions that comprise a sufficient number of a T cell to be suitable as an adoptive immunotherapeutic. The claimed compositions comprise a first isolated T cell expressing a T cell receptor specific for an MHC-peptide complex containing a housekeeping epitope. In some embodiments, the claimed compositions further comprise a second isolated T cell population, wherein the first and second T cell populations recognize two different housekeeping epitopes. Accordingly, Claim 1 recites a composition comprising a sufficient number of a first isolated T cell to be suitable as an adoptive immunotherapeutic. Claims 2-5, 29-36 and 40-41 depend from independent Claim 1 and thus contain all the features thereof as well as additional features recited within the claims. Claim 42 recites a composition comprising at least a first and a second isolated T cell population, wherein said first population comprises a sufficient number of a first T cell to be suitable as an adoptive immunotherapeutic for an animal, and wherein said second population comprises a sufficient number of a second T cell to be suitable as an adoptive immunotherapeutic for an animal. Claims 43-52 and 55-57

depend from independent Claim 42 and thus contain all the features thereof as well as additional features recited within the claims.

A. The Combination of Zajac and Kawakami Fails to Render the Invention Obvious

The Examiner relies on Zajac to teach T cell lines that recognize a particular epitope associated with MART-1/ Melan-A_{27-35}, while Kawakami is relied upon to teach that tumor-reactive T cells can be expanded *in vitro* and used for adoptive transfer.

Zajac discloses the construction of a replication-deficient recombinant vaccinia virus (rVV) encoding Mart-1/Melan-A_{27-35} (rVV-M) and suggests that the reagent could be used in MART-1/ Melan-A-TAA-based active immunotherapy. Following construction of rVV-M, the ability of the virally expressed epitope to expand specific CTL was assessed using tumor-infiltrating lymphocytes (TILs) from melanoma patients and peripheral-blood mononuclear cells (PBMC) of healthy donors. The reference discloses that rVV-M was able to induce specific CTL following two stimulation rounds from one out of three melanoma-derived TIL and that MART-1/Melan-A_{27-35} specific cytotoxic activity could be generated in PBMC from three out of three healthy donors following two stimulation rounds. However, as Applicants successfully argued to overcome the rejection under 35 U.S.C. 102(b) in view of this reference, the T cells ultimately derived by Zajac are not suitable for adoptive administration to a human because during generation of MART-1/Melan-A_{27-35}-specific CTLs, the T cells were exposed to agents that would then be present in the compositions, thus rendering the compositions unsuitable for adoptive administration to a human.

With regard to the instant rejection under 35 U.S.C. 103, the Examiner notes that TILs isolated from melanoma patients were able to specifically lyse target cells (pages 492-493 and Figure 2 in particular). The Examiner takes the position that the TILs qualify as being "isolated from an immunized animal" because they were obtained from melanoma patients and were therefore "immunized" to the antigen by the presence of the tumor in the body, and that: "prior to transformation of the cell line the reactive T cells were present in the human serum, a carrier suitable for administration to a human." Office Action, page 3. The Examiner argues that "it would have been well within the purview of the artisan at the time the invention was made to expand tumor-reactive T cells in *in vitro* culture and make the cells suitable for administration as

an adoptive immunotherapeutic reagent." Thus, in attempting to build the instant *prima facie* case of obviousness, the Examiner seeks to disregard the explicit teachings of Zajac, and instead limit its focus on particular research materials—freshly isolated TILs from melanoma patients used to test the active immunotherapeutic reagent described therein. This line of reasoning cannot establish a case of obviousness.

While the Examiner is correct in stating that TILs isolated from melanoma patients were able to specifically lyse target cells (pages 492-493 and Figure 2 in particular), Applicants note that this was following *in vitro* immunization and not following "immunization" by the presence of tumor in the body, as the Examiner suggests. Specifically, Zajac teaches that the active immunotherapeutic product disclosed therein (rVV-M) was able to induce specific CTL following two stimulation rounds from one out of three melanoma-derived TILs. Moreover, Zajac explicitly teaches that T cells reactive to MART-1/Melan-A_{27-35} are undetectable in freshly isolated TILs from melanoma patients. *See* Zajac at page 493, first column ("No cytotoxic activity specific for the MART-1/Melan-A_{27-35} was detectable in any culture before initiation of the CTL induction experiments."). Thus, at the point in time where the Examiner would qualify the TILs as being "isolated from an immunized animal" and ready to expand, Zajac explicitly teaches that the TILs showed no evidence of MART-1/MelanA_{27-35} specific CTL activity until after *in vitro* stimulation with rVV-M. There is no teaching or suggestion to use the TILs for any purpose beyond assessing the properties of the reagent disclosed therein, and certainly not for use in the development of an adoptive immunotherapeutic. Thus, a person of ordinary skill in the art would not understand the disclosure of Zajac to teach or suggest a composition comprising a first isolated T cell to be suitable as an adoptive immunotherapeutic, wherein said T cell expresses a T cell receptor specific for an MHC-peptide complex comprising a first housekeeping epitope.

Accordingly, it would not be readily apparent to one of ordinary skill in the art how to apply the teachings of Kawakami to the research tools of Zajac, as suggested by the Examiner, to obtain a composition comprising a sufficient number of a first isolated T cell expressing a T cell receptor specific for an MHC-peptide complex containing a housekeeping epitope. That is, the teachings of the secondary reference cannot be applied to the TILs used in the testing of the

reagent developed in Zajac with any reasonable expectation of success in arriving at the claimed invention.

Moreover, even if the cited references could be combined in the manner suggested by the Examiner, which Applicants do not concede, neither reference teaches or suggests any recognition of the value of making a composition suitable for adoptive administration to a human comprising a sufficient number of a first isolated T cell that expresses a T cell receptor specific for an MHC-peptide complex comprising a **housekeeping epitope**, and as such, the combined teachings do not provide any guidance with respect to how to arrive at each and every element of the claimed invention. Applicants remind the Examiner that the claims are not drawn to T cells specific for a particular epitope sequence, rather the claims are drawn, in relevant part, to **T cells specific for a housekeeping epitope**.

The instant application teaches that a housekeeping epitope is a polypeptide fragment that is an MHC epitope, and that is displayed on a cell in which housekeeping proteasomes are predominantly active. The inventors of the instant application recognized that there are two types of proteasomes with distinct subunit compositions that degrade cytosolic proteins in a cell: housekeeping proteasomes and immunoproteasomes. These distinct proteasomes exert their cleavage function to produce two classes of polypeptide fragments: housekeeping epitopes (polypeptide fragments that are MHC epitopes and are displayed on cells in which housekeeping proteasomes are predominantly active) or immune epitopes (polypeptide fragments that are MHC epitopes and are displayed on cells in which immunoproteasomes are predominantly active). The **housekeeping proteasome** is constitutively active in **peripheral cells and tissues** of the body. Whereas, the **immunoproteasome** is constitutively active in **professional antigen presenting cells (pAPCs)**. Consequently, certain diseased cells present peptides derived from housekeeping proteasome activity and can avoid surveillance by the immune system, which searches for peptides derived from immunoproteasome activity. This differential proteolytic activity can explain why certain diseases seem impervious to the controls of the immune system. It is because of this differential activity that a pAPC may not present crucial epitopes presented by target cells expressing the mismatched proteasome.

Any suggestion to combine the references to arrive at an adoptive immunotherapeutic comprising a T cell specific for a housekeeping epitope derives from the teachings of the instant

application, which is impermissible hindsight reconstruction. Thus, the Examiner has clearly used the present application as a template to piece together prior art teachings to allege obviousness.

Finally, it appears that the Examiner may be using an inherency analysis in an obviousness determination. In particular, the Examiner appears to be arguing that by applying the teachings of Kawakami to the research tools disclosed by Zajac, one might arrive at a T cell that is specific for MART-1/Melan-A_{27-35} that might inherently anticipate a T cell to be suitable as an adoptive immunotherapeutic, wherein said T cell expresses a T cell receptor specific for an MHC-peptide complex comprising a **housekeeping epitope**. However, "[o]bviousness cannot be predicated on what is not known at the time an invention is made, even if the inherency of a certain feature is later established." M.P.E.P. 2141.02(V) citing *In re Rijckaert*, 9 F.2d 1531 (Fed. Cir. 1993). Inherency is immaterial if the record establishes that one of ordinary skill in the art would not appreciate or recognize that inherent result. *In re Shetty*, 566 F.2d 81, 86 (CCPA 1977) citing *In re Naylor*, 369 F.2d 765, 768 (CCPA 1966). In fact, courts have routinely held that "the inherency of an advantage and its obviousness are entirely different questions. That which may be inherent is not necessarily known." *In re Spormann*, 363 F.2d 444, 448 (CCPA 1966); *In re Naylor*, 369 F.2d 765, 768 (CCPA 1966); *In re Shetty*, 566 F.2d 81, 86 (CCPA 1977).

While this may be an inherent feature of the asserted adoptive immunotherapeutic if it were to be made (and Applicants emphatically do not concede that it would be made based on the cited disclosures for at least the reasons stated above), it is a feature that was not known or appreciated prior to the disclosure of the instant specification. That is, even if the cited references could be combined to teach a first isolated T cell suitable for use as an adoptive immunotherapeutic, wherein said T cell expresses a T cell receptor specific for MART-1/Melan-A_{27-35}, the combination would not make the claims obvious because the recited feature of a T cell receptor specific for an MHC-peptide complex comprising a first housekeeping epitope, as claimed, was not a recognized or intended objective. Applicants respectfully submit that in the instant case, the claimed feature of the genus of T cells specific for housekeeping epitopes was not recognized in the cited art, and as such, obviousness cannot be predicated on the cited

combination of references. Furthermore, the unappreciated features of a species do not make obvious a genus defined by those features.

Moreover, the Federal Circuit has held that "[i]nherency . . . may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient [to establish inherency]." *In re Oelrich*, 666 F.2d 578, 581-82 (Fed. Cir. 1981). "Such a retrospective view of inherency is not a substitute for some teaching or suggestion supporting an obviousness rejection. *In re Rijckaert*, 9F.3d 1531 1534 (Fed. Cir. 1993) *citing In re Newell*, 891 F.2d 899, 901 (Fed. Cir. 1989). The formation of such a reagent by happenstance based on the combination of references that do not provide any specific teachings or guidance to do so is not the same as recognizing its importance and seeking its isolation or inclusion in a therapeutic formulation. In contrast, Applicants were the first to recognize that T cells specific for housekeeping epitopes could be useful in an adoptive immunotherapy protocol.

Finally, the M.P.E.P. states that "if the prior art merely discloses compounds as intermediates in the production of a final product, one of ordinary skill in the art would not ordinarily stop the reference synthesis and investigate the intermediate compounds with an expectation of arriving at claimed compounds which have different uses." M.P.E.P. 2144.09 VI *citing In re Lalu*, 747 F.2d 703, 223 USPQ 1257 (Fed. Cir. 1984).

Similar to "intermediates" in the synthesis of a compound, the isolated TILs are an intermediate research tool in the development and characterization of the active immunotherapeutic disclosed in Zajac. Within the art, none of the references teaches using the sera containing T cells without further manipulation. Accordingly, one of ordinary skill in the art would not have stopped to pursue the use of such cells in the production of an adoptive immunotherapeutic. Thus, a *prima facie* case of obviousness cannot be established under the applicable legal doctrine.

For at least the foregoing reasons, Applicants respectfully submit that a *prima facie* case of obviousness has not been established and that the pending claims are patentable over the cited combination of references. Withdrawal of this rejection is thus respectfully requested.

B. The Combination of Kittlesen and Kawakami Fails to Render the Invention Obvious

The Office Action relies on Kittlesen, like Zajac above, to teach T cell lines that recognize a particular epitope, in this instance an epitope derived from tyrosinase. Kawakami is again relied upon, as above, to teach that tumor-reactive T cells can be expanded *in vitro* and used for adoptive transfer. For the same reasons expressed above, this combination of references also fails to render the instant invention obvious.

Kittlesen teaches direct isolation of T cells from patients, wherein the T cells are cultured *in vitro* and repeatedly stimulated with autologous tumor cells. Kittlesen is silent as to the frequency of epitope-reactive T cells in the starting materials, and Kittlesen does not teach or suggest that the isolated T cells have been activated *in vivo* prior to isolation. Moreover, no tyrosinase activity is reported for T cells directly obtained from melanoma patients.

As with the rejection above, the Office Action makes the supposition that one of skill would read Kittlesen and depart from any teachings beyond the isolation of T cells from patients. For the reasons discussed above with respect to the combination of Zajac and Kawakami, this reasoning fails to support a legal finding of obviousness because the same deficiencies found in Zajac and Kawakami are also present in the combination of Kittlesen and Kawakami.

For at least the foregoing reasons, Applicants respectfully submit that a *prima facie* case of obviousness has not been established and that the pending claims are patentable over the cited combination of references. Withdrawal of this rejection is thus respectfully requested.

C. The Combination of Jäger and Kawakami Fails to Render the Invention Obvious

As with Kittlesen and Zajac above, the Office Action relies on Jäger to teach T cell lines that recognize a particular epitope, in this instance an epitope derived from NY-ESO-1. Kawakami is again relied upon, as above, to teach that tumor-reactive T cells can be expanded *in vitro* and used for adoptive transfer. For the reasons expressed above, this combination of references also fails to render the instant invention obvious.

Jäger teaches direct isolation of cells from a patient and establishment of a stable T cell line. To obtain the CTL line, Jäger cultured mixed lymphocyte tumor cell cultures of peripheral blood lymphocytes (PBLs) and an autologous donor cell line. The reference only discloses NY-

ESO-1 reactive T cells *after* mixing lymphocyte tumor cell cultures of PBLs and the tumor cell line described therein.

Thus, the same deficiencies found in the combinations of Zajac and Kawakami and Kittlesen and Kawakami are also present in the combination of Jäger and Kawakami.

For at least the foregoing reasons, Applicants respectfully submit that a *prima facie* case of obviousness has not been established and that the pending claims are patentable over the cited combination of references. Withdrawal of this rejection is thus respectfully requested.

D. The Combination of Zajac, Jäger, Kawakami and Tsuji Fails to Render the Invention Obvious

The Office Action relies on Tsuji to teach "immunizing a subject with multiple peptides derived from [] melanoma cells," while Zajac, Jäger and Kawakami are all relied upon for the same reasons as described above.

Claims 45-52 and 54-59 recite, in relevant part, "wherein the first T cell expresses a T cell receptor specific for a first MHC-peptide complex comprising a first housekeeping epitope … and wherein the second T cell expresses a T cell receptor specific for a second MHC-peptide complex comprising a second housekeeping epitope . . . ." Applicants submit that in addition to the deficiencies noted above with respect to a housekeeping epitope, the recognition of more than one *housekeeping* epitope by more than one isolated T cell is absent in the prior art, and thus the invention as a whole is unobvious.

The Office Action states "Tsuji teaches that the peptides were acid eluted from cultured tumor cells. Acid elution removes peptides from MHC class I on the surface of cells, meaning that these peptides from non-immune cells (the B16F1 melanoma line) are the product of processing by standard proteasomes and therefore are housekeeping epitopes."

First, it is important to recognize that non-immune cells can and do express the immunoproteasome. *See*, for example, Specification as filed, Page 22. Secondly, and specific to the cell line used by Tsuji, it had been reported in the art, at the time of filing, that multiple components of the MHC class I antigen processing pathway are defective in this cell line. Seliger *et al.*, "Characterization of the Major Histocompatiblity Complex Class I Deficiencies in B16 Melanoma Cells" *Cancer Res.* (2001) 61:1095-1099. Accordingly, because antigen

processing in this cell line was considered to be defective, one of skill in the art would not have looked to the Tsuji cell line as a source of epitopes to treat clinical (as opposed to model) tumors. Even if Tsuji were considered to inherently disclose housekeeping epitopes, the reference provides no guidance that these are the epitopes that one should target in adoptive immunotherapy. To the contrary, as discussed above, a person of ordinary skill in the art would have been disinclined to look to the Tsuji cell lines as a source of desirable epitopes or T cells.

Furthermore, Tsuji immunizes with an eluted peptide preparation that the Examiner presumes to contain multiple peptides. However, even granting the presumption, *arguendo*, one must still take into account immunodominance effects that can occur with mixed immunogens. In view of possible immunodominance, there is no reasonable expectation that the T cell response obtained from such immunization necessarily (or even likely) contained T cells recognizing more than one MHC-peptide complex comprising an epitope derived from a target antigen. Likewise there is nothing in the data presented in Tsuji that supports a conclusion of MHC-peptide complexes comprising multiple epitopes. Thus, Tsuji neither inherently embodies multiple T cell specificities, not does it suggest an adoptive therapeutic targeting multiple epitopes.

The failings of Zajac, Jäger and Kawakami, as described in the prior sections, are not cured by the teachings of Tsuji. Accordingly, the combination of Zajac, Jäger and Kawakami, and Tsuji does not render the claimed invention obvious.

For at least the foregoing reasons, Applicants respectfully submit that a *prima facie* case of obviousness has not been established and that the pending claims are patentable over the cited combination of references. Withdrawal of this rejection is thus respectfully requested.

CONCLUSION

Applicants submit that the present Application is in condition for allowance and respectfully request the same. If any issues remain, the Examiner is cordially invited to contact Applicants' representative at the number provided below in order to resolve such issues promptly.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 04-0258.

Respectfully submitted,
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